

WHAT IS CLAIMED IS:

1. A method of treating a vaso-occlusive event, the method comprising:
 - (a) diagnosing a subject in need of treatment for a vaso-occlusive event; and
 - (b) administering to the subject a combination comprising a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof
- 5 and a selective serotonin reuptake inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.
2. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC₅₀ to COX-2 IC₅₀ not less than about 50.
3. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC₅₀ to COX-2 IC₅₀ not less than about 100.
4. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, deracoxib, valdecoxib, rofecoxib, lumiracoxib, etoricoxib, meloxicam, parecoxib, 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide, 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one, N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide, 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, 2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid, (3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone, and (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.
5. The method of claim 1 wherein the selective serotonin reuptake inhibitor is selected from the group consisting of citalopram, fluoxetine, fluvoxamine, paroxetine, escitalopram oxalate, sertraline, norfluoxetine and N-demethylsertraline.
6. The method of claim 4 wherein the selective serotonin reuptake inhibitor is selected from the group consisting of citalopram, fluoxetine, fluvoxamine, paroxetine, escitalopram oxalate, sertraline, norfluoxetine and N-demethylsertraline.
7. The method of claim 1 wherein the vaso-occlusive event is selected from the group consisting of myocardial infarction, stroke, amaurosis fugax, aortic stenosis, cardiac stenosis, carotid artery stenosis, coronary stenosis and pulmonary stenosis.

8. The method of claim 6 wherein the vaso-occlusive event is selected from the group consisting of myocardial infarction, stroke, amaurosis fugax, aortic stenosis, cardiac stenosis, carotid artery stenosis, coronary stenosis and pulmonary stenosis.

9. The method of claim 7 wherein the cyclooxygenase-2 selective inhibitor is celecoxib and the selective serotonin reuptake inhibitor is sertraline.

10. A method of treating a vaso-occlusive event, the method comprising:

(a) diagnosing a subject in need of treatment for a vaso-occlusive event; and

(b) administering to the subject a combination comprising a selective serotonin

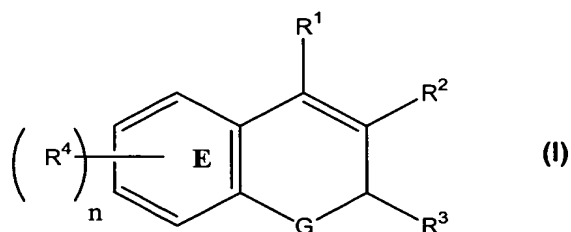
reuptake inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof

5 and a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein the cyclooxygenase-2 selective inhibitor is a chromene compound, the chromene compound comprising a benzothiopyran, a dihydroquinoline or a dihydronaphthalene.

11. The method of claim 10 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC_{50} to COX-2 IC_{50} not less than about 50.

12. The method of claim 10 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC_{50} to COX-2 IC_{50} not less than about 100.

13. The method of claim 10 wherein the cyclooxygenase-2 selective inhibitor is a compound having the formula



wherein:

n is an integer which is 0, 1, 2, 3 or 4;

G is O, S or NR^a ;

R^a is alkyl;

R^1 is selected from the group consisting of H and aryl;

R^2 is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

10 R^3 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

each R^4 is independently selected from the group consisting of H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, 15 alkylamino, arylamino, aralkylamino, heteroarylamine, heteroarylalkylamine, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; and 20 R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

14. The method of claim 13 wherein:

n is an integer which is 0, 1, 2, 3 or 4;

G is O, S or NR^b ;

R^1 is H;

5 R^b is alkyl;

R^2 is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

R^3 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl, wherein haloalkyl, alkyl, aralkyl, cycloalkyl, and aryl each is independently optionally 10 substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and

each R^4 is independently selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamine, heteroarylalkylamine, nitro, amino, 15 aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or wherein R^4 together with ring E forms a naphthyl radical.

15. The method of claim 13 wherein:

n is an integer which is 0, 1, 2, 3 or 4;

G is oxygen or sulfur;

R¹ is H;

5 R² is carboxyl, lower alkyl, lower aralkyl or lower alkoxycarbonyl;

R³ is lower haloalkyl, lower cycloalkyl or phenyl; and

each R⁴ is H, halo, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy,

lower alkylamino, nitro, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered

heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower

10 aralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, 6-membered-nitrogen containing heterocyclosulfonyl, lower alkylsulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, or lower alkylcarbonyl; or

wherein R⁴ together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

16. The method of claim 13 wherein:

R² is carboxyl;

R³ is lower haloalkyl; and

each R⁴ is H, halo, lower alkyl, lower haloalkyl, lower haloalkoxy, lower alkylamino,

5 amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, lower alkylsulfonyl, 6-membered nitrogen-containing heterocyclosulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, or lower alkylcarbonyl; or

R⁴ together with ring E forms a naphthyl radical.

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17. The method of claim 10 wherein the cyclooxygenase-2 selective inhibitor is (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.

18. The method of claim 10 wherein the selective serotonin reuptake inhibitor is selected from the group consisting of citalopram, fluoxetine, fluvoxamine, paroxetine, escitalopram oxalate, sertraline, norfluoxetine and N-demethylsertraline.

19. The method of claim 13 wherein the selective serotonin reuptake inhibitor is selected from the group consisting of citalopram, fluoxetine, fluvoxamine, paroxetine, escitalopram oxalate, sertraline, norfluoxetine and N-demethylsertraline.

20. The method of claim 17 wherein the selective serotonin reuptake inhibitor is selected from the group consisting of citalopram, fluoxetine, fluvoxamine, paroxetine, escitalopram oxalate, sertraline, norfluoxetine and N-demethylsertraline.

21. The method of claim 17 wherein the selective serotonin reuptake inhibitor is sertraline.

22. The method of claim 10 wherein the vaso-occlusive event is selected from the group consisting of myocardial infarction, stroke, amaurosis fugax, aortic stenosis, cardiac stenosis, carotid artery stenosis, coronary stenosis and pulmonary stenosis.

23. The method of claim 19 wherein the vaso-occlusive event is selected from the group consisting of myocardial infarction, stroke, amaurosis fugax, aortic stenosis, cardiac stenosis, carotid artery stenosis, coronary stenosis and pulmonary stenosis.

24. The method of claim 21 wherein the vaso-occlusive event is selected from the group consisting of myocardial infarction, stroke, amaurosis fugax, aortic stenosis, cardiac stenosis, carotid artery stenosis, coronary stenosis and pulmonary stenosis.

25. A method of treating a vaso-occlusive event, the method comprising:

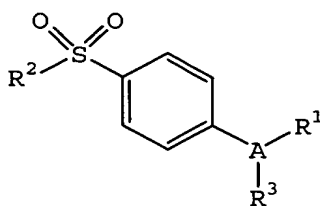
- (a) diagnosing a subject in need of treatment for a vaso-occlusive event; and
- (b) administering to the subject a combination comprising a selective serotonin

reuptake inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof
5 and a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein the cyclooxygenase-2 selective inhibitor is a tricyclic compound, the tricyclic compound comprising a benzenesulfonamide or methylsulfonylbenzene.

26. The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC_{50} to COX-2 IC_{50} not less than about 50.

27. The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC_{50} to COX-2 IC_{50} not less than about 100.

28. The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor is a compound of the formula:



wherein:

A is selected from the group consisting of partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

R¹ is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R¹ is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxy carbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

R² is selected from the group consisting of methyl or amino; and

R³ is selected from the group consisting of a radical selected from H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocycloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxy carbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxy carbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N- arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N- aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N- arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N- arylaminosulfonyl.

29. The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, valdecoxib, parecoxib, deracoxib, rofecoxib,

etoricoxib, and 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

30. The method of claim 25 wherein the selective serotonin reuptake inhibitor is selected from the group consisting of citalopram, fluoxetine, fluvoxamine, paroxetine, escitalopram oxalate, sertraline, norfluoxetine and N-demethylsertraline.

31. The method of claim 28 wherein the selective serotonin reuptake inhibitor is selected from the group consisting of citalopram, fluoxetine, fluvoxamine, paroxetine, escitalopram oxalate, sertraline, norfluoxetine and N-demethylsertraline.

32. The method of claim 29 wherein the selective serotonin reuptake inhibitor is selected from the group consisting of citalopram, fluoxetine, fluvoxamine, paroxetine, escitalopram oxalate, sertraline, norfluoxetine and N-demethylsertraline.

33. The method of claim 29 wherein the selective serotonin reuptake inhibitor is sertraline.

34. The method of claim 25 wherein the vaso-occlusive event is selected from the group consisting of myocardial infarction, stroke, amaurosis fugax, aortic stenosis, cardiac stenosis, carotid artery stenosis, coronary stenosis and pulmonary stenosis.

35. The method of claim 31 wherein the vaso-occlusive event is selected from the group consisting of myocardial infarction, stroke, amaurosis fugax, aortic stenosis, cardiac stenosis, carotid artery stenosis, coronary stenosis and pulmonary stenosis.

36. The method of claim 32 wherein the vaso-occlusive event is selected from the group consisting of myocardial infarction, stroke, amaurosis fugax, aortic stenosis, cardiac stenosis, carotid artery stenosis, coronary stenosis and pulmonary stenosis.

37. A method of treating a vaso-occlusive event, the method comprising:

(a) diagnosing a subject in need of treatment for a vaso-occlusive event; and

(b) administering to the subject a combination comprising a selective serotonin

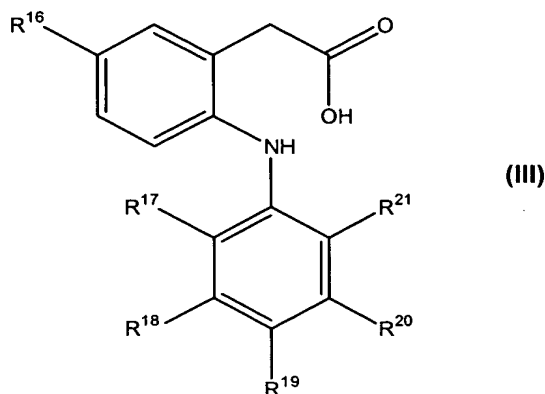
reuptake inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof

5 and a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein the cyclooxygenase-2 selective inhibitor is a phenyl acetic acid compound.

38 The method of claim 37 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC_{50} to COX-2 IC_{50} not less than about 50.

39. The method of claim 37 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC_{50} to COX-2 IC_{50} not less than about 100.

40. The method of claim 37 wherein the cyclooxygenase-2 selective inhibitor is a compound having the formula:



wherein:

R^{16} is methyl or ethyl;

R^{17} is chloro or fluoro;

R^{18} is hydrogen or fluoro;

R^{19} is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

R^{20} is hydrogen or fluoro;

R^{21} is chloro, fluoro, trifluoromethyl or methyl; and

provided that R^{17} , R^{18} , R^{19} and R^{20} are not all fluoro when R^{16} is ethyl and R^{19} is H.

41. The method of claim 40 wherein:

R^{16} is ethyl;

R^{17} and R^{19} are chloro;

R^{18} and R^{20} are hydrogen; and

and R^{21} is methyl.

42. The method of claim 37 wherein the selective serotonin reuptake inhibitor is selected from the group consisting of citalopram, fluoxetine, fluvoxamine, paroxetine, escitalopram oxalate, sertraline, norfluoxetine and N-demethylsertraline.

43. The method of claim 40 wherein the selective serotonin reuptake inhibitor is selected from the group consisting of citalopram, fluoxetine, fluvoxamine, paroxetine, escitalopram oxalate, sertraline, norfluoxetine and N-demethylsertraline.

44. The method of claim 41 wherein the selective serotonin reuptake inhibitor is sertraline.

45. The method of claim 42 wherein the vaso-occlusive event is selected from the group consisting of myocardial infarction, stroke, amaurosis fugax, aortic stenosis, cardiac stenosis, carotid artery stenosis, coronary stenosis and pulmonary stenosis.

46. The method of claim 44 wherein the vaso-occlusive event is selected from the group consisting of myocardial infarction, stroke, amaurosis fugax, aortic stenosis, cardiac stenosis, carotid artery stenosis, coronary stenosis and pulmonary stenosis.

47. A method of treating a vaso-occlusive event, the method comprising:

(a) diagnosing a subject in need of treatment for a vaso-occlusive event; and

(b) administering to the subject a combination comprising a cyclooxygenase-2

selective inhibitor selected from the group consisting of celecoxib, deracoxib, valdecoxib, rofecoxib, lumiracoxib, etoricoxib, parecoxib, 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, and (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid; and

a selective serotonin reuptake inhibitor selected from the group consisting of citalopram, fluoxetine, fluvoxamine, paroxetine, escitalopram oxalate, sertraline, norfluoxetine and N-demethylsertraline.

48. The method of claim 47 wherein the cyclooxygenase-2 selective inhibitor is celecoxib.

49. The method of claim 47 wherein the cyclooxygenase-2 selective inhibitor is deracoxib.

50. The method of claim 47 wherein the cyclooxygenase-2 selective inhibitor is valdecoxib.

51. The method of claim 47 wherein the cyclooxygenase-2 selective inhibitor is rofecoxib.

52. The method of claim 47 wherein the cyclooxygenase-2 selective inhibitor is etoricoxib.
53. The method of claim 47 wherein the cyclooxygenase-2 selective inhibitor is parecoxib.
54. The method of claim 47 wherein the cyclooxygenase-2 selective inhibitor is 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.
55. The method of claim 47 wherein the cyclooxygenase-2 selective inhibitor is (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.
- 56 The method of claim 47 wherein the cyclooxygenase-2 selective inhibitor is lumiracoxib.
56. The method of claim 47 wherein the vaso-occlusive event is selected from the group consisting of myocardial infarction, stroke, amaurosis fugax, aortic stenosis, cardiac stenosis, carotid artery stenosis, coronary stenosis and pulmonary stenosis.